

REMARKS

Rejection under 35 U.S.C. §101, first paragraph

The rejection of claims 1, 2 and 13 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

Applicants traverse this rejection for the reasons submitted below.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed

invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a “nebulous expression” such as “biological activity” or “biological properties” that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be “substantial.” *Brenner*, 383 U.S. at 534. A “substantial” utility is a practical, “real-world” utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a “well-established” utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no “well-established” utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II Applicants have established that one skilled in the art would understand that there is a “well-established” utility for the claimed invention

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. The uses of TCRLP for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, e.g., ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary

skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

[T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease are “well-established” utilities for the claimed invention

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 2, submitted February 26, 2002):

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Reference No. 2, submitted February 26, 2002), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 3, submitted February 26, 2002); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 4, submitted February 26, 2002).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 5, submitted February 26, 2002) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.
- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.
- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

These real-world uses, particularly toxicology testing, are explained in detail in the Furness Declaration (submitted February 26, 2002), the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

C. The Furness Declaration is submitted in support of "well-established" utilities of TCRLP.

Although, the Office has acted to "enter" the Furness Declaration (Office Action of September 9, 2002, p. 2, ¶1.), the Office has refused consideration of the Furness Declaration, allegedly because: Mr. Furness's interest in the outcome of the case, as an employee of the assignee, "cannot be considered impartial" and further, the Office alleges that it was not "submitted by one recognized as an expert in the art." Furthermore, the declaration was dismissed by the Office because it "provides no additional factual support for the assertion that the **EST** of the instant claims is expressed as a T cell receptor beta chain protein" (emphasis added, Office Action, p. 2-3, ¶ 4). Applicants respectfully request reconsideration of the Furness Declaration for the reasons provided below.

1. The Furness Declaration is submitted in support of the utility of SEQ ID NO:1

The Declaration of Lars Michael Furness provides direct proof of the utility of the claimed invention. The Declaration describes some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application.

The Furness Declaration was also submitted to corroborate Applicants' established, real world utility for the instant invention in toxicology testing, disease diagnosis and drug development. The Examiner's assumption that the Declaration could only be probative if it provided "*factual* support for the assertion that the . . . instant claims is expressed as a T cell receptor beta chain protein" (Office Action of September 9, 2002, p. 3) is incongruous with the

reason for submitting the Furness Declaration. As stated by Mr. Furness on page 3; ¶ 5 of the Furness Declaration:

I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Hillman '940 application and its parent, the Hillman '097 application, does not disclose a substantial, specific and credible "real-world" utility for the SEQ ID NO:1 polypeptide and (b) to state and explain the bases for any conclusions I reach.

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its function. But as stated above, the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 11). Such uses of the claimed invention in 2-D PAGE gels and western blots to assess expression and toxicity of SEQ ID NO:1 are "real-world" utilities which are credible, specific and substantial utilities attributable to the claimed invention.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

2. Mr. Furness is an Expert in the Field

The Office has apparently refused to consider the objective evidence provided by the Furness Declaration because in part, the declaration was is allegedly not "submitted by one recognized as an expert in the art" (Office Action, September 9, 2002; pages 2-3; ¶ 4). The

Office further questions whether Mr. Furness meets Webster's definition of "expert" by stating that:

an expert must be established as significantly more skilled even than one of skill in the art. In the biological sciences, where one of skill in the art often has at least doctoral level training, one with mastery of the subject would necessarily have at least that level of training, and additionally, some demonstration of said mastery such as a body of peer-reviewed publications, i.e., a significant *curriculum vitae* . . . the declarant has provided a brief *resume* indicating just a bachelor's level of education and no peer-reviewed publications. Thus, it is unclear how the declarant can be considered an expert in the field encompassed by the instant claims. (Office Action, September 9, 2002; page 2; ¶ 4).

By stating that "one of skill in the art often has at least doctoral level training" (emphasis added) the Office recognizes that an advanced degree is not an absolute requirement for one to be skilled in the art to which the invention pertains. Therefore, the academic degrees obtained by Mr. Furness cannot be used as an absolute bar to consideration of Mr. Furness' expert opinions. Applicants request the Office to provide the citation within the MPEP identifying the qualifications required of an "expert" or that an advanced degree is a requirement for qualification as an expert or for the matter, that an "expert" is required when submitting a Declaration under 37 CFR 1.132 for the reasons Applicants are submitting this Declaration.

Furthermore, the Office is incorrect in asserting that Mr. Furness does not have the publication record commensurate to "one of skill in the art." Mr. Furness has authored or co-authored at least the following original articles:

- a) Furness, L.M., Analysis of gene and protein expression for drug mode of toxicity, Current Opinion in Drug Discovery and Development, 5, 98-103 (2002);
- b) Furness, L.M., Henrichwark, S., Egerton, M., Expression databases – resources for pharmacogenomic R&D, Pharmacogenomics, 1, 281-288 (2000);
- c) Kinloch, R.A., Treherne, J.M., Furness, L.M., Hajimohamadreza, I., The pharmacology of apoptosis, Trends in Pharmacological Sciences, 20, 35-42 (1999);

- d) Bailey, D.S., Furness, L.M., Dean, P.M., New tools for quantifying molecular diversity, Pharmainformatics: A Trends Guide, 4, 6-9 (1999);
- e) Bailey, D.S., Bondar, A., Furness, L.M., Pharmacogenomics – it's not just pharmacogenetics, Current Opinion in Biotechnology, 9, 595-601 (1998); and
- f) Schwinn, D.A., Johnston, G.I., Page, S.O., Mosley, M.J., Wilson, K.H., Worman, N.P., Campbell, S., Fidock, M.D., Furness, L.M., Parry-Smith, D.J., Cloning and pharmacological characterization of human alpha-1 adrenergic receptors: Sequence corrections and direct comparison with other species homologues, Journal of Pharmacology and Experimental Therapeutics, 272, 134-142 (1995).

These publications provide objective evidence that Mr. Furness is significantly more skilled than one of skill in the art. The fact that editors of leading journals in the field have published articles authored or co-authored by Mr. Furness indicates that he is considered to not only be "one of skill in the art," but that he is one with mastery of the subject.

Additionally, in failing to consider the probative value of the Furness Declaration, the Office has failed to consider Mr. Furness' practical real-world work experience that objectively demonstrates that he is "significantly more skilled than one of ordinary skill in the art." For example, Mr. Furness discloses in the Furness Declaration that he has been doing real-world research on the sequencing, synthesis, and analysis of nucleic acids and proteins since 1985 (Furness Declaration at pages 1-2, ¶ 2). Thus, he has first-hand knowledge of the state of the art at the time the application was filed. Mr. Furness states that for at least two years, he directed a program to "use microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improving drug design and development" (Furness Declaration at page 2, ¶ 2). Therefore, he is an expert on the use of microarray and protein expression data, and is able to provide objective evidence as to the real-world utilities of expressed proteins. For at least the above reasons, Mr. Furness is "significantly more skilled than one of ordinary skill in the art" and the substance of his Declaration should be given full consideration by the Patent Office.

3. The Examiner Misinterprets the Objectivity of Furness

Moreover, the Office has refused consideration of the Furness Declaration in part, allegedly because Mr. Furness's interest in the outcome of the case, as an employee of the assignee, "cannot be considered impartial." Applicants respectfully disagree with the Office's position and request consideration of the Furness Declaration.

The Office concludes that because Mr. Furness was at the time of signing the declaration "an employee of the assignee, Mr. Furness's opinion (expert or otherwise) cannot be considered impartial." However, the MPEP also states that, "[a]n affidavit of an applicant as to the advantages of his or her claimed invention, while less persuasive than that of a disinterested person, cannot be disregarded for this reason alone. *Ex parte Keyes*, 214 USPQ579 (Bd. App. 1982); *In re McKenna*, 203F.2d 717, 97 USPQ 348 (CCPA 1953). M.P.E.P. 716.01 (c). Mr. Furness is not an applicant of the instant invention and therefore, a "decided interest in the outcome of the case" is not relevant as alleged by the Office (Office Action, September 9, 2002; page 3; ¶ 4).

The policy of the Patent Office in considering affidavits or declarations traversing rejections is that "[e]vidence traversing rejections must be considered whenever present." M.P.E.P. § 716.01 (emphasis added). Thus, the Declaration of Lars Michael Furness, being entered and therefore, properly of record, must now be considered.

Applicants reiterate the arguments presented in the Brief on Appeal of February 26, 2002; and the objective evidence of the Furness Declaration. Applicants hereby request consideration of these arguments and the Furness Declaration, and withdrawal of this rejection under 35 U.S.C. § 101. Such withdrawal is merited, for example, by the well-established utilities of the claimed invention in toxicology testing and drug discovery.

4. The Furness Declaration provides evidence that the claimed polypeptide can be useful for a number of gene and protein expression monitoring applications.

The Office Action has failed to consider the objective evidence presented in the Furness Declaration, that there is at least one well-established utility for the claimed invention that would have been understood by one of skill in the art at the time of the priority date of the instant application. The Furness Declaration shows that the claimed polypeptides and compositions have utilities in toxicology testing and drug discovery regardless of knowing the biological

function of the claimed polypeptide, and that these utilities would have been understood by one of skill in the art before July 18, 1997.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Hillman '097 application on July 18, 1997 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, *e.g.*, ¶¶ 11-14). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 11.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

In view of the Hillman '097 application, the Wilkins article, and other related pre-July 1997 publications, persons skilled in the art on July 18, 1997 clearly would have understood the Hillman '097 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below. (Furness Declaration, ¶ 10)

* * *

Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer and autoimmune disorders, for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26, submitted February 26, 2002).

5. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), **in particular genes having medical and pharmaceutical significance such as the instant sequence**. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become

even more powerful tools. Thus, the claimed invention adds more than incremental benefit to the drug discovery and development process.

D. The uses of TCRLP in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Examiner rejected the claims at issue on the grounds that the use of an invention as tool for research is not a “substantial” use, e.g., that “Basic research such as studying the properties of the claimed product itself or mechanisms in which the material is involved would be required” (Office Action, filed 10/24/00, p. 4). Because the Examiner’s rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact “useful” in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO’s actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO’s Training Materials to be useful.

The subset of research uses that are not “substantial” utilities is limited. It consists only of those uses in which the claimed invention is to be an object of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit

on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. (“What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.”) Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a “substantial utility.” These include: screening libraries of pharmaceutical agents to identify those which specifically bind TCRLP in a variety of drug screening techniques; generating antibodies which specifically bind and can identify TCRLP; and titration of TCRLP to initially determine the effective dose in cell culture assays or in animal models.

III. Applicants’ evidence that the claimed invention is a member of the T-cell receptor polypeptide family would be clear and convincing evidence to one skilled in the art

A. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polypeptide is a member of T-cell receptor polypeptide family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the T-cell receptor polypeptide family to TCRLP. In the Office Action of September 9, 2002, the Patent Examiner takes the position that unless Applicants can establish the expression of TCRLP or identify which particular biological

function within the class of T-cell receptor beta polypeptides is possessed by TCRLP, utility cannot be imputed (Office Action of September 9, 2002, page 3, ¶ 4). To demonstrate utility by membership in the class of T-cell receptor beta polypeptides, the Examiner would require that all T-cell receptor beta polypeptides possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner v. Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g., Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).¹

The Examiner has not provided any evidence that any member of the T-cell receptor polypeptide family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the T-cell receptor polypeptide family, useful.

Even if the Examiner's "common utility" criterion were correct, the T-cell receptor polypeptide family would meet it. It is undisputed that known members of the T-cell receptor polypeptide family function in antigen recognition in cells and in the transmission of activation signals to initiate cell-mediated reactions. A person of ordinary skill in the art need not know any more about how the claimed invention functions in antigen recognition in cells and in the

¹At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

transmission of activation signals to initiate cell-mediated reactions to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given T-cell receptor beta polypeptide functions in antigen recognition in cells and in the transmission of activation signals to initiate cell-mediated reactions. The Examiner then goes on to assume that the only use for TCRLP absent knowledge as to how this member of the T-cell receptor polypeptide family actually works is further study of TCRLP itself. However, this assumption is incorrect.

As disclosed by Applicants, knowledge that TCRLP is a T-cell receptor beta-like polypeptide is more than sufficient to make it useful for the diagnosis and treatment of cancer and autoimmune disorders. Indeed, TCRLP has been shown to be expressed in fetal and immune cell libraries. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

B. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility beyond the reasonable probability required by law.

Because there is a substantial likelihood that the claimed TCRLP is functionally related to T-cell receptor beta polypeptide, a polypeptide of undisputed utility, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

In this regard, TCRLP is homologous to two human T-cell receptor beta-like polypeptides that are both essential components of a T-cell receptor complex. In particular, TCRLP shares more than 80% sequence identity over 314 amino acid residues, and is in fact nearly 100% identical with the two proteins in the C-terminal half of the protein (about 150 amino acid residues) (see specification, p. 14, and Figures 2A and 2B).

This is more than enough homology to demonstrate a reasonable probability that the utility of the human T-cell receptor beta polypeptides can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Response to Office Action, filed 1/24/00, Exhibit 1). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to the human T-cell receptor beta polypeptides is, accordingly, very high.

The Examiner must accept the Applicants' demonstration that the homology between the claimed invention and T-cell receptor beta polypeptides demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:1 in the patent application and referred to as TCRLP in the application. Applicants have disclosed by more than reasonable probability that TCRLP is a member of the T-cell receptor polypeptide family, and that the T-cell receptor polypeptide family includes T-cell receptors, each of which functions in antigen recognition in cells and in the transmission of activation signals to initiate cell-mediated reactions.

The Examiner must accept the applicant's demonstration that the claimed polypeptide is a member of T-cell receptor polypeptide family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

C. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground

that the applicant cannot impute utility to the claimed invention based on its 80-85 % homology to another polypeptide undisputed by the Examiner to be useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

The literature cited by the Examiner *infra* is not inconsistent with the Applicants' proof of homology by a reasonable probability. It may show that Applicants cannot prove function by homology with **certainty**, but Applicants need not meet such a rigorous standard of proof.

Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. See *In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

In the present case, the Office Action alleges that the amino acid sequence identity between TCRLP and known T-cell beta receptor proteins is insufficient to establish that TCRLP is a member of the T-cell receptor family of proteins because "there is no recognition in the art that sequence identity predicts biological function and therefore a disclosure of sequence identity does not lead one of skill in the art to believe said identity gives credible use to the claimed protein" (Office Action, filed 10/24/00, p. 3). The cited literature identifies some of the difficulties that may be involved in predicting protein function, though none suggest that functional homology cannot be inferred by a reasonable probability in this case. See Mikayama et al.(1993), Voet et al.(1990), Bork (2000), Atwood (2000), and Skolnick et al.(2000), in Office Actions, filed 10/24/00 and 4/04/01. Importantly, all of these documents fail to support the outstanding rejections, and none contradict Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well (see Response to Office Action, filed 1/24/01, p. 4-5). At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The Examiner cites Mikayama et al. as evidence that a single amino acid residue difference between two proteins (here, MIF and GIF) can lead to differences in function. MIF and GIF, however, are not different proteins. MIF and GIF have been shown to be encoded by identical genes and thus to have identical amino acid sequences. Watarai, H. et al.

(2000; Proc. Natl. Acad. Sci. USA 97:13251-13256) state that “[g]lycosylation inhibiting factor (GIF) and macrophage migration inhibitory factor (MIF) share an identical structure gene.” (See abstract, page 13251.) Further, Watarai et al. state that “[a]fter molecular cloning of this cytokine [GIF], however, we realized that the sequence of the coding region of human GIF cDNA (6) was identical to the sequence of human MIF cDNA (7), except one base. In the human genomes, Paralkar and Wistow (reference #8 of Watari et al.) identified only one functional MIF-like gene, whose predicted transcript sequence agreed exactly with that of MIF cDNA, indicating that the one base difference between GIF and MIF cDNA is due to an error in sequencing.” (See page 13251, column 1, first paragraph.) It is noted that the Watarai et al. paper is from the some of the same authors (Kimishige Ishizaka, Yasuyuki Ishii) as the Mikayama paper. The differences in activity between MIF and GIF have been shown to result from differences in post-translational modification, not in sequence, though both indeed function as cytokines. Hence, the Examiner’s use of Mikayama et al. as a document purporting to show that single amino acid differences result in differences in function is incorrect. It is noted in any case that changes in function of proteins due to post-translational modifications and/or single amino acid substitutions are far and away the exception, not the rule, and one of skill in the art would not reasonably doubt the asserted imputed utility of TCRLP based on its similarity with human T-cell receptor beta protein.

Likewise, the Examiner’s citation of Voet et al. and the fact that a single amino acid change in hemoglobin causes sickle-cell anemia is again a case of the exception not the rule. The fact that the sickle-cell mutation has been perpetuated is a fluke of nature due only to the fact that it confers an advantage (immunity to malaria) in heterozygous carriers. Generally, without such coincidence, the sickle-cell gene would have been selected against, because it causes a disease that disadvantages the carrier. Without this extraordinary twist of fate, the mutant gene would have been eliminated many generations ago. One can hardly expect this sort of serendipity to be a frequent occurrence, “rescuing” genes with mutations in key functional areas that would otherwise be eliminated. In the present case, for TCRLP, there is absolutely no reason to assume that the protein of SEQ ID NO:1 possesses any mutation in a key functional region (and it is the Examiner’s burden in any case to show that this is more likely than not).

The Examiner further relied on the teachings of Bork, Atwood and Skolnick et al. regarding the alleged unpredictability of current methods of comparative sequence analysis. Applicants respectfully suggest that the Examiner attempts to draw too sweeping a conclusion from Bork, Atwood, and Skolnick et al. It may be true that the use of sequence analysis to predict protein function is not 100% accurate (although still, based upon Bork's figure of 70% accuracy, more likely than not to be correct) as the quality of data in the public sequence databases is still insufficient to annotate perfectly every new sequence. However, this is a general conclusion; one of skill in the art would clearly understand that the likelihood of a prediction being correct for a particular sequence depends upon how much data is available for the particular family to which it belongs.

The Examiner's reference to Atwood teaching an error rate >80% in predicting protein structure/function appears to be drawn from the following statement:

In "predicting" genes, protein functions, and structures, it is helpful to define our terms precisely and be honest about our achievements. Otherwise, we will continue to be baffled by paradoxical new prediction methods that yield >80% error rates. (Atwood, page 473, first column.)

Atwood's statements (and indeed the entire Atwood document) mention several types of prediction analysis, that of genes, protein functions, and structures. Atwood does not specify which are the "paradoxical new prediction methods" that yield the ">80% error rates" and whether these rates apply to predictions of genes, protein function, or structures, or to some or all of the above. Indeed, Atwood does not describe **any** error rate for the method used in the present application (e.g., BLAST analysis) to ascribe T-cell beta receptor activity to TCRLP based on sequence similarity to a human T-cell receptor beta protein.

The Examiner also draws too sweeping a conclusion from the statements in the Skolnick et al. document. Careful reading of the statements that the Examiners quotes and paraphrases show the lack of applicability to the instant invention. First, Skolnick et al. state, with respect to the use of sequence analysis to predict protein function, that "[b]oth the alignment and the motif methods are powerful but a recent analysis has demonstrated their significant limitations¹⁵, suggesting that these methods will increasingly fail as the protein-sequence databases become more diverse." The Examiner has not shown, and Skolnick et al. do not assert, that the methods used in the present application to ascribe T-cell receptor beta activity to TCRLP based on

sequence similarity to a human T-cell receptor beta protein result in mis-analysis of the claimed polypeptide sequences and indeed that any alleged “limitations” outweigh the “powerful” nature of the methods. The Examiner quotes Skolnick et al. that “inaccurate use of the sequence-to-function” methods has led to significant functional-annotation errors in the sequence databases.” However, the Examiner provides no evidence that any “inaccurate use of the sequence-to-function methods” was made in the present invention. Again, sweeping conclusions, without any analysis of the data actually present in the instant application, do not constitute either evidence or sound scientific reasoning to show that a person of ordinary skill in the art would reasonably doubt Applicants’ invention lacked patentable utility.

The Office’s attention is further directed to Brenner et al., *supra* that teaches through exhaustive analysis of a data set of proteins with **known** structural and functional relationships and with <40% overall sequence identity, that 30% identity has been determined to be a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) As shown in the Figures and as discussed in the specification, SEQ ID NO:1 shares 80-85% identity with at least two known T-cell receptor beta proteins over at least 300 residues, and nearly 100% identity over 150 residues, vastly exceeding this threshold. Since these criteria are based on a data set of known homologous proteins with shared structural and functional features, one of ordinary skill in the art would reasonably expect the polypeptides of the invention possess the evolutionarily conserved **structural and functional** characteristics of a T-cell receptor beta protein.

This assertion is further supported by the teachings of Bowie et al. (Response to Office Action, filed 1/24/00, Exhibit 2). Bowie teaches that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution. (Bowie et al., page 1306, 1st column, last paragraph, and 2nd column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph.) It is known in the art that natural selection acts to conserve protein function. As taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are usually eliminated by natural selection. Based on these central tenets of molecular evolution,

Applicants put forth that the amino acid differences among Applicant's polypeptide and the known T-cell receptor beta proteins, are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would therefore conclude that, more likely than not, the level of conservation observed between Applicant's polypeptide and the two known human T-cell receptor beta proteins is indicative of a common function, and hence common utility, among these proteins.

The preponderance of evidence therefore does not support the Examiner's basis for the rejection of claims under 35 U.S.C. § 101. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the claimed polypeptide is in fact a member of the T-cell receptor family of proteins, which are known to have specific utility.

IV. The diagnosis and treatment of cancer and autoimmune disorders are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. Additionally, these uses are explained, in detail, in the Furness Declaration accompanying the Brief on Appeal filed February 2, 2002, discussed *supra*. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

The specification teaches that TCRLP is a member of the T-cell receptor polypeptide family and that defects in T-cell receptor genes, T-cell receptor expression and in T-cell subtype population levels have been found in lymphomas, leukemias, allergic responses, and in autoimmune and immunodeficiency disorders (see specification, p. 14, lines 5-8; and p. 2, lines 26-28). Applicants have presented evidence that the claimed invention would have the utilities of T-cell receptor beta proteins, proteins which are known to be involved in cancer and immune disorders. Therefore, one of ordinary skill in the art would conclude that, more likely than not,

that TCRLP would also have these uses. Thus, the claimed invention meets the utility requirements under 35 U.S.C. §§ 101 and 112, first paragraph.

V. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections. To the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: “specific” utilities, which meet the statutory requirements, and “general” utilities, which do not. The Training Materials define a “specific utility” as follows:

A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as “gene probe” or “chromosome marker” would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between “specific” and “general” utilities by assessing whether the asserted utility is sufficiently “particular,” *i.e.*, unique (Training Materials at p.52) as compared to the “broad class of invention.” (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) (“With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.”).)

Such “unique” or “particular” utilities never have been required by the law. To meet the utility requirement, the invention need only be “practically useful,” *Natta*, 480 F.2d 1 at 1397, and confer a “specific benefit” on the public. *Brenner*, 383 U.S. at 534. Thus incredible “throwaway” utilities, such as trying to “patent a transgenic mouse by saying it makes great snake food,” do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where “specific utility” is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be “definite,” not particular. *Montedison*, 664 F.2d at 375. Applicant is not aware of any court that has rejected an assertion of utility on the grounds that it is not “particular” or “unique” to the specific invention. Where courts have found utility to be too “general,” it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had “useful biological activity” was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a “particular” type of cancer was determined to satisfy the specificity requirement). “Particularity” is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of “general” utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to

be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus, the Training Materials cannot be applied consistently with the law.

VI. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be withdrawn.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Applicants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of “lack of specificity,” as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, “like a nose of wax,”² to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be withdrawn.

²“The concept of patentable subject matter under §101 is not ‘like a nose of wax which may be turned and twisted in any direction * * *.’ *White v. Dunbar*, 119 U.S. 47, 51.” (*Parker v. Flook*, 198 USPQ 193 (US SupCt 1978))

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Rejection under 35 U.S.C. §112, first paragraph

Claim 2 stands rejected under the first paragraph of 35 U.S.C. §112 for allegedly containing subject matter “not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.” It is asserted at page 4 of the September 9, 2002 Office Action that “said claim still encompasses a virtually unlimited number of proteins while the specification still provides an insufficient written description of said proteins.

A. Legal Requirements

. . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the “written description” inquiry, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office’s own “Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1”, published January 5, 2001, which provide that:

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics⁴² which provide evidence that applicant was in possession of the claimed invention,⁴³ i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.⁴⁴ What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.⁴⁵ If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.⁴⁶

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

B. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The subject matter recited in claim 2 is adequately disclosed in the Specification given what is conventional or well known to one skilled in the art.

Please note that the “variant” language of independent claim 2 recites, “[a] variant of T-cell receptor beta-like protein having at least 90% amino acid identity to SEQ ID NO:1 and which retains IL-2 inducing activity.” It is submitted that the Specification provides an adequate written description of the claimed variants of SEQ ID NO:1 to convey with reasonable clarity to those skilled in the art that applicants were in possession of the invention as claimed at the time of the filing of this application.

Variants of SEQ ID NO:1 are defined in the Specification at, for example, page 7, lines 4-11; and page 14, lines 26-30. Polypeptide sequence variants are known by one of skill in the art to have amino acid substitutions which do not alter the function of the polypeptide. For example, a change of an amino acid residue to another at the extreme amino- or the carboxy-terminus of the sequence most likely will not alter the function of the polypeptide. The Specification defines specific structural domains related to TCRLP proteins at page 14, lines 16-23. Structural domains within TCRLP include four potential caseine kinase II phosphorylation sites and five potential protein kinase C phosphorylation sites that function within the signaling cascades initiated by T-cell receptor (TCR) activation to receive co-stimulatory signals through other surface receptors and through which signal transduction pathways are activated. Analysis of the functional domains found in the homologs of TCRLP; gi 1100182, SEQ ID NO:3 and gi 339012; SEQ ID NO:4 indicate the presence of immunoglobulin domains (Exhibits A and B, respectively, enclosed herewith). These same domains are also found within SEQ ID NO:1 as seen in the alignment of all three TCR proteins presented in Figure 2. Accordingly, it is well within the skill of those in this art to identify those polypeptides comprising an amino acid sequence at least 90%

identical to the amino acid sequence of SEQ ID NO:1 and that these polypeptide variants retain the IL-2 inducing activity.

Furthermore, an assay to measure IL-2 inducing activity is defined in the specification at pages 50-51, Example X. Assays to determine functional activity are considered routine experimentation when identifying functional sequence variants. One of ordinary skill in the art would recognize polypeptide sequences which are variants having at least 90% amino acid identity to SEQ ID NO:1, as those polypeptide sequences which, when assayed, have IL-2 inducing activity. Accordingly, polypeptides comprising an amino acid sequence that is 90% identical to the amino acid sequence of SEQ ID NO:1 can easily be identified by one of skill in the art based on both the presence of functional and structural domains and by the assay, all disclosed in the Specification. Accordingly, Applicants have disclosed the claimed invention in sufficient detail and provided identifying characteristics such that the skilled artisan would understand that Applicants were in possession of the claimed invention. Therefore, the specification provides an adequate written description of the claimed variants of SEQ ID NO:1 to convey with reasonable clarity to those skilled in the art that applicants were in possession of the invention as claimed at the time of the filing of this application. Therefore, Applicants respectfully request withdrawal of this rejection.

The Office has Erred in Evaluating Applicants' Claimed Invention

Applicants bring to the Office's attention an error in interpreting the instant claims of the subject application. Applicants are concerned with a written statement made by the Examiner, "the assertion that the EST of the instant claims is expressed as a T cell receptor beta chain protein" (emphasis added, Office Action, p. 2-3, ¶ 4). Applicants respectfully bring to the Office's attention that the "instant claims" encompass *inter alia* a full-length coding region of a gene expressing a full length polypeptide. Should the Examiner continue to insist that Applicants' claims are to an EST, Applicants request the Examiner provide evidence as to where in the instant specification support for this assertion is found, and if there is no such support, to withdraw the assertion in a written statement.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 621-8555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 09-0108.

Respectfully submitted,
INCYTE GENOMICS, INC.

Date: 09, December 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph(s) beginning at line 15 of page 43 has been amended as follows:

The TONGTUT01 cDNA library was constructed from tongue tumor tissue obtained from a 36-year-old Caucasian male [(specimen #0065B; Mayo Clinic, Rochester MN)] during a hemiglossectomy. The pathology report indicated recurrent invasive grade 2 squamous-cell carcinoma forming a mass 2.5 x 2 x 1.3 cm in the right tongue.